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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/549,871	09/16/2005	Andreas Kunkel	128100-00126-US	2451
23416 7590 02/12/2007 CONNOLLY BOVE LODGE & HUTZ, LLP P O BOX 2207 WILMINGTON, DE 19899			EXAMINER MEAH, MOHAMMAD Y	
			ART UNIT	PAPER NUMBER
			1652	
SHORTENED STATUTORY PERIOD OF RESPONSE		MAIL DATE	DELIVERY MODE	
3 MONTHS		02/12/2007	PAPER	

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

# Office Action Summary

Application No.

10/549,871

Applicant(s)

KUNKEL ET AL.

Examiner

Mohammad Meah

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 17 November 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1-30 is/are pending in the application.
- 4a) Of the above claim(s) 11-14, 10-22, 25--28 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-10, 15-18, 23-24 and 29 is/are rejected.
- 7) ☐ Claim(s) 1-10, 23, 24 and 29 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

## Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

## Attachment(s)

- ☐ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☒ Information Disclosure Statement(s) (PTO/SB/08).  
Paper No(s)/Mail Date 09/16/05.
- ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_
- ☐ Notice of Informal Patent Application
- ☐ Other: \_\_\_\_\_

### **DETAILED ACTION**

Applicant, on date 11/17//2006 elected with traverse Group II (claims 1-10, 15-18, 23-24 and 29) for examination.

#### ***Election/Restriction***

Applicant, on date 11/17//2006 elected with traverse Group II (claims 1-10, 15-18, 23-24 and 29), drawn to process of producing ergosta-5,7 dienol by culturing organisms having decreased desaturase activity and increased HMG-CoA reductase activity, which is, expressed squalene epoxidase of SEQ ID NO:8. for examination. Groups I and III-V (claims 1-30) of election/restriction-office action of date 10/17/2006 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions.

Applicant's election with traverse of group II (claims 1-10, 15-18, 23-24 and 29), in the reply filed on 11/17//2006 is acknowledged. Applicants argue that there would be no undue burden on the examiner to examine all the claims. This is not persuasive because while the search for each of these distinct groups would be overlapping it would not be coextensive. Art that applies for microorganisms, DNA, vector method of using them, etc may or may not be relevant to the others.

The requirement is still deemed proper and is therefore made FINAL.

#### ***Priority***

Acknowledgement is made of applicant's PCT priority date based on application filing date of 03/12/2004 of PCT/EP04/02582 and foreign applications Germany 103 12314.8 filed on date 03/19/2003.

### ***Objections***

Claims 1-10, 23-24 and 29 are objected having non elected matters.

Appropriate correction is required. Claim 29 depends on a non-elected claim.

They must be dependent from an elected claim. Claims 9 and 17 are objected for poor grammar. Appropriate correction is required.

### ***Claim Rejections***

#### ***35 U.S.C 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-10, 15-18, 23-24 and 29 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 the recitation of " biosynthetic intermediates and or metabolites" makes the claim indefinite as it is unclear what is (are) the biosynthetic intermediates and or metabolites it refers to.

Claims 1, 2, 4, 5 and 15 the recitation of " wild type" makes these claims indefinite as it is unclear what this wild type is referred to it the wild type DNA or protein or organism?

**35 U.S.C 112 1ST paragraph Rejections**

*Written Description requirement Rejections:*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10, 15-18, 23-24 and 29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-10, 15-18, 23-24 and 29 are directed to a process of producing ergosta-5,7 dienol or any biosynthetic intermediates and /or metabolites thereof by culturing organisms having a decreased desaturase activity, an increased HMG-CoA reductase activity and overexpression of the squalene epoxidase of SEQ ID NO:8.or a variant thereof from any source. The specification fails to describe in any fashion the physical and/or chemical properties of the claimed class of biosynthetic intermediates and /or metabolites thereof or class of ergosterol-biosynthetic enzymes including squalene epoxidase other than its involvement in ergosterol biosynthetic pathway. No relation between the structure of the species and function is described. Neither the structure of the

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compounds produced in the method of using organisms nor the structure of genes expressed in the organism are defined in the specification. The specification discloses only a few DNA of the claimed genus of desaturase, HMG-CoA reductase and squalene epoxidase (i.e., SEQ ID Nos : 2, 4, 8) expressed in the microorganism for the production of few ergosterol compounds ( i.e., lanosterol, Zymosterol, 4,4 dimethyl-zymosterol), which are insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

***Enablement Rejections:***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10, 15-18, 23-24 and 29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process of producing ergosta-5,7 dienol or any biosynthetic intermediates and /or metabolites by culturing organisms having decreased desaturase activity and increased HMG-CoA reductase activity which overexpress squalene epoxidase of SEQ ID NO:8, as shown in example 1, does not reasonably provide

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enablement for process of producing ergosta-5,7 dienol, or any biosynthetic intermediates and /or metabolites thereof by culturing organisms having decreased desaturase activity and increase of any HMG-CoA reductase activity which overexpress any squalene epoxidase or squalene epoxidase having 30% sequence identity to SEQ ID NO:8. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, make and for use the invention commensurate in scope with these claims.

Claims 1-10, 15-18, 23-24 and 29 are so broad as to encompass any process of producing ergosta-5,7 dienol, or any biosynthetic intermediates and /or metabolites by culturing organisms having decreased desaturase activity and increase of any HMG-CoA reductase activity which overexpress any squalene epoxidase or squalene epoxidase having 30% sequence identity to SEQ ID NO:8. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number processes of producing ergosta-5,7 dienol or any biosynthetic intermediates and /or metabolites thereof by culturing organisms having decreased desaturase activity and increase of any HMG-CoA reductase activity which overexpress any squalene epoxidase or squalene epoxidase having 30% sequence identity to SEQ ID NO:8 broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance

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with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to a process of producing ergosta-5,7 dienol by culturing organisms having decreased desaturase activity of a few desaturases and increase of a few HMG-CoA reductases and overexpression of squalene epoxidase ( SEQ ID Nos:2, 4, 8, 10, 12, etc).

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable (e.g., Whisstock, et al. Quarterly Rev. Biophy. 2003, 36, pp 307-340). In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass any process of producing ergosta-5,7 dienol by culturing organisms having decreased desaturase activity and increase of any HMG-CoA reductase activity and overexpression of any squalene epoxidase or squalene epoxidase having 30% sequence identity to SEQ ID NO:8 because the specification does not establish: (A) regions of the protein structure which may be modified without effecting desaturase, HMG-CoA reductase and squalene epoxidase activity; (B)



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the general tolerance of desaturase, HMG-CoA reductase and squalene epoxidase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any desaturase, HMG-CoA reductase squalene or epoxidase residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any process of producing ergosta-5,7 dienol by culturing organisms having decreased desaturase activity and increase of any HMG-CoA reductase activity which overexpress any squalene epoxidase or squalene epoxidase having 30% sequence identity to SEQ ID NO:8 polypeptide with an enormous number of modifications of amino acid residues of a protein having amino acid sequence of SEQ ID NO: 8. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of squalene epoxidase, having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

**CLAIM Rejection - 35 U.S.C 102**

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-8, 15-16, 23-24 and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Saunders et al. ( EP 0486290 –IDS reference). Saunders et al. teach methods of making ergosta-5,7 dienol using various mutant *S. cerevisiae* strains, with reduce expression of desaturase, increased expression of squalene epoxidase, that are further transformed with a gene encoding HMG-CoA reductase activity.

Claims 1-8, 15-16, 23-24 and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Weber et al. (WO-99/16886–IDS reference). Weber et al. teach methods of making ergosta-5,7 dienol using various mutant *S. cerevisiae* strains with reduce expression of desaturase and increased expression of squalene epoxidase and HMG-CoA reductase.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mohammad Meah whose telephone number is 571-272-1261. The examiner can normally be reached on 8:30-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is

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assigned is 703-872-9306. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system.

Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Mohammad Younus Meah, PhD

Examiner, Art Unit 1652

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